Evaluation of anaesthesia with xylazine-ketamine and xylazine-fentanyl-ketamine in rabbits:A comparative study

ABSTRACT

Clinical and serum biochemical markers were utilized to assess the clinical efficacy of routinely used preanaesthetics and induction agents in rabbits. Eight healthy rabbits (3.0-3.5kg) of either sex were randomly assigned to one of two groups: XK (Xylazine-ketamine) or XFK (Xylazine–fentanyl–ketamine). Intramuscular injections of xylazine (5 mg/kg), ketamine (35 mg/kg), and fentanyl (0.02 mg/kg) were given to rabbits. Clinical parameters (rectal temperature, heart rate, and respiratory rate), as well as reflexes (righting reflex, palpebral reflex, and pedal reflex), were measured before and after anaesthetic injection at 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 minutes. Blood samples were also taken before anaesthesia and 30 minutes following induction. An autoanalyzer was used to examine serum biochemical parameters. In the XFK group, we observed that rectal temperature increased considerably ($P<0.05$) at 20 and 30 minutes after induction and then gradually fell to preanaesthetic control values. During the anaesthetic phase, both groups' heart rates and respiration rates reduced significantly. In XK-injected rabbits, the return of righting reflexes was delayed. Surgical anaesthesia lasted much longer in the animals of XK groups. During surgical anaesthesia, the values of albumin, cholesterol, phosphorus, HDL, and LDL were significantly increased ($P<0.05$) after administration of XK, whereas the values of total protein, globulin, cholesterol, triglyceride, creatinine, HDL, potassium, and chloride were significantly decreased ($P<0.05$). The XK combination provided sufficient anaesthesia for rabbits, as evidenced by a prolonged anaesthetic period, and good cardiovascular and other clinical indices.

Keywords: Anaesthesia, clinical chemistry, fentanyl, ketamine, rabbit, xylazine

INTRODUCTION

Rabbits are frequently employed as animal models in a variety of medical and veterinary procedures, including experimental surgery and biomedical research (Kihç, 2004). Because the difference between surgical anaesthesia and respiratory arrest is so small, they are the most difficult laboratory animals to anesthetize (Kamal et al., 2019). The susceptibility of the rabbit respiratory center to the depressive effects of anaesthetic regimens has been blamed for the high rate of death during rabbit anaesthesia (Kaya et al., 2002). Anesthesia is used for a range of surgical operations, including sedation for blood collection (since rabbits become nervous while being handled), intravenous cannula installation, and other operating measures like neutering, gastrotomy, cystotomy, and fracture fixation (Brodbelt, 2009). When all safety precautions are performed, such as using the correct anesthetics and following the specified dosing schedule, administering anesthetics to rabbits is deemed safe.

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Research Article

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In rabbit anaesthesia, xylazine and ketamine are commonly used anaesthetics (Oguntoye and Oke, 2014). When ketamine is employed as the sole anesthetic agent, hypertonus, inadequate muscular relaxation, persistent pain reflex responses, and violent recovery from anaesthesia occur (Chen et al., 2015), necessitating the inclusion of preanesthetic drugs. Pre-anesthetics are also used in conjunction with general anesthetics; in most species, xylazine hydrochloride is used to reduce stress, relax the animal, and minimize the overall dose of general anesthetics. Fentanyl citrate is an opioid agonist with high potency (Kaya et al., 2002). Although it can produce marked respiratory depression, it only causes minor alterations in circulatory variables. The respiratory depressive effect of fentanyl, like that of longer-lasting opioid analgesics, may last longer than the analgesic effect (Dupras et al., 2001). Injectable anaesthetics are extensively used in rabbits because they are simple to administer. They can be administered intravenously, intramuscularly, intraperitoneally, or subcutaneously. Based on the foregoing information, we set out to conduct this study with the following goals: to compare the clinical effects of the tested anaesthetic combinations (xylazine-ketamine and xylazine-fentanyl-ketamine); to assess reflex responses and anaesthetic indices, and to investigate changes in serum biochemical parameters during anaesthesia.

MATERIAL and METHOD

This study compared the effects of two different anesthetic combinations in New Zealand White Rabbits. Animal Welfare and Experimentation Ethics Committee (AWEEC) of the Faculty of Veterinary Science, Bangladesh Agricultural University (BAU), Mymensingh offered recommendations for the study.

Experimental Animals

Eight clinically healthy White New Zealand rabbits of either sex, weighing roughly 3.0 to 3.5 kg and aged between 8 and 10 months, were used in this investigation and were obtained from a local market in Mymensingh. The rabbits were given a 7-day acclimatization period in the Department of Medicine, Faculty of Veterinary Science, BAU's experimental shed. Individual wooden-wire cages with controlled environmental conditions were employed to house the rabbits (temperature, relative humidity, air changes, and light). Seasonal fresh grass, fresh vegetables, commercial rabbit feed, and ad libitum water were supplied to the rabbits. Food, but not drink, was put on hold for 12 hours before the trial began.

Experimental Design

The rabbits in the experiment were randomly allocated into two groups, each with four rabbits. The anaesthetics were given out in the following order: Group XK: Xylazine-Ketamine and Group XFK: Xylazine-Fentanyl-Ketamine.

Group XK

For anaesthesia, the animals in group XK were injected with xylazine hydrochloride (Xyla®, Interchmie Pharmaceuticals, Holland) and ketamine hydrochloride (Ketalar®, Popular Pharmaceuticals, Tongi, Bangladesh). Xylazine hydrochloride was given intramuscularly at a dose rate of 5 mg/kg. After 15 minutes, ketamine hydrochloride was delivered intramuscularly at a dose rate of 35 mg/kg.

Group XFK

Xylazine (Xyla®, Interchmie Pharmaceuticals, Holland), Fentanyl (Fentanyl Citrate®, Martindale Pharmaceuticals, Romford, UK), and Ketamine (Ketalar®, Popular Pharmaceuticals, Tongi, Bangladesh) were used to anesthetize this group of animals. Xylazine hydrochloride was delivered intramuscularly at a dose rate of 5 mg/kg, fentanyl was injected intramuscularly at a dose rate of 0.02 mg/kg BW, and ketamine hydrochloride was injected intramuscularly at a dose rate of 35 mg/kg BW after 15 minutes of fentanyl administration.

Anesthetic Procedure

The animal was placed on the surgical table in a dorsal posture before anaesthesia. The anaesthetic drugs were given intramuscularly using 1 ml and 3 ml disposable plastic syringes, where the animals were gripped by an assistant. Puncture of the needle and observation of distinct reflexes results verified induction.

Clinical Evaluation

Before the injection (0 minutes) and at 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 minutes following the injection of the anesthetic agent, heart rate, respiration rate, and body temperature were measured. Following the injection, the depth of anaesthesia was measured using the righting reflex, palpebral reflex, and pedal reflexes at 10-minute intervals until the anaesthesia was terminated in all groups. The time between the injection of the induction agent and the disappearance of the righting reflex was used to calculate the induction time. The capacity of the animal to reestablish the righting reflex was used to assess recovery following anaesthetic.

Clinical Examination of Temperature, Respiratory Rate, and Heart Rate

A stethoscope was placed on the lower left lateral thoracic wall to assess the heart rate. The body temperature was recorded using a thermometer and the respiratory rate was determined using a stethoscope by measuring the chest movement of the thoraco-abdomen.

Clinical Examination of Reflexes

The rabbit's righting reflex was assessed by timing how long it took it to move from dorsal to sternal recumbency. When no response was elicited by stroking the dorsal eyelid with a cotton-tip applicator, the palpebral reflex was reported as missing. The pedal reflexes were checked by pinching the fore limb and hind limb with a needle (right and left).

Collection of Blood Sample

Each experimental animal had three ml of blood drawn through jugular venipuncture with a 3 ml disposable syringe, which was immediately transferred to a vacutainer (clot activator tube) for serum separation and biochemical analysis.

Biochemical Examinations

Blood samples were centrifuged for 15 minutes at 3000 rpm after one hour. For biochemical analysis, the supernatant serum was collected in an Eppendorf tube using a micropipette. Total Protein (TP), Albumin, Globulin, Cholesterol, Triglyceride (TG), Calcium (Ca), Phosphorus (P), High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), Creatinine, Sodium, Potassium, and Chloride were all measured in the serum samples. The serum biochemistry was measured using a photometric approach utilizing a T80 UV/VIS Spectrometer (USA) at the Mohammad Hossain Central Laboratory, BAU, Mymensingh.

Statistical Analysis

All the data was presented as Mean ± SEM (Standard Error of Mean). Statistical Package for the Social Sciences (SPSS) version 20.0 was used to compare data within and across groups using one-way ANOVA (Analysis of Variance). Probability $P<0.05$ or less was considered as statistically significant.

RESULTS

Effect of Different Anaesthetic Combinations on Clinical Parameters in Rabbit Effect on Rectal Temperature (RT)

We found no significant changes in rectal temperature in the animals of group XK at different time intervals in this investigation. Rectal temperature in the animals of group XFK, on the other hand, was considerably higher at 20 and 30 minutes compared to the preanaesthetic control value (Figure 1).

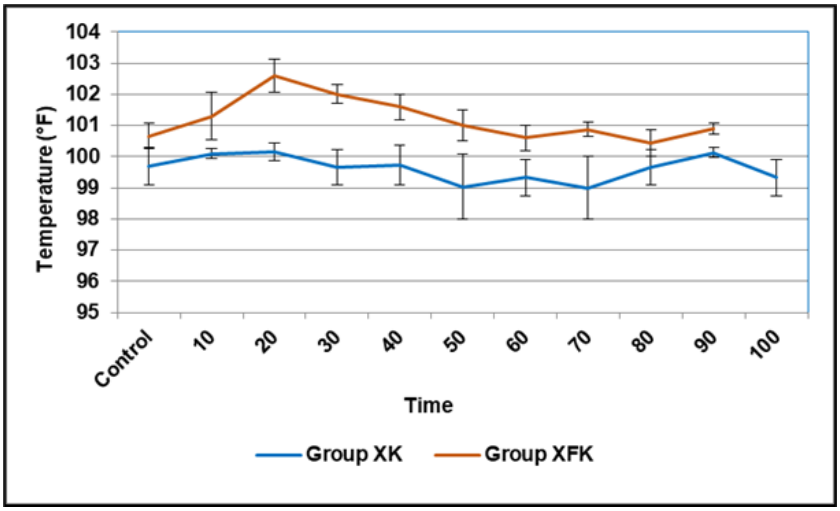

Figure 1. Effects of different anaesthetic combinations on body temperature**.**

Effect on Heart Rate (HR)

We found significant (P<0.05) variations in heart rate in group XK animals at different time intervals during the anaesthetic period when compared to the preanaesthetic control value. In the animals of group XFK, the heart rate declined considerably (P<0.05) at 40 and 50 minutes, then increased significantly (P<0.05) at 60 minutes, then decreased significantly (P<0.05) as compared to the preanaesthetic control value (Figure 2).

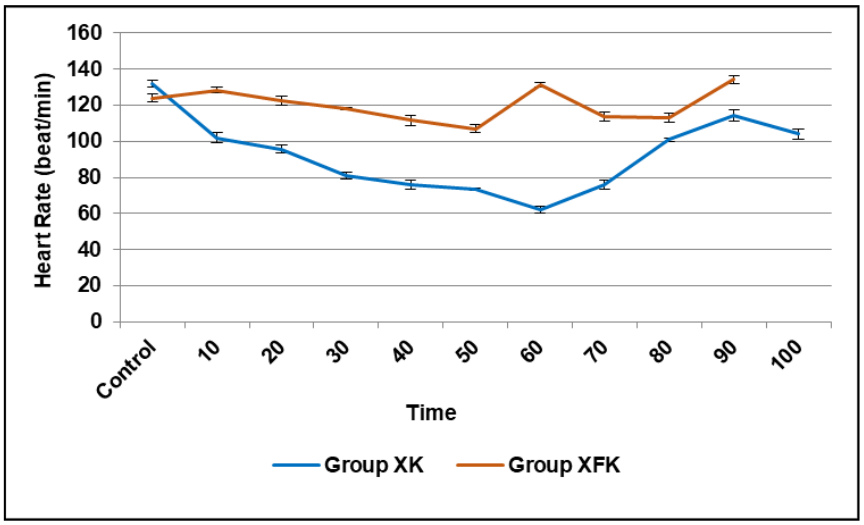

Figure 2. Effects of different anaesthetic combinations on heart rate.

Effect on Respiratory Rate (RR)

The respiratory rate in the animals of groups XK and XFK was significantly (P<0.05) altered throughout the study period when compared to the preanaesthetic control values (Figure 3).

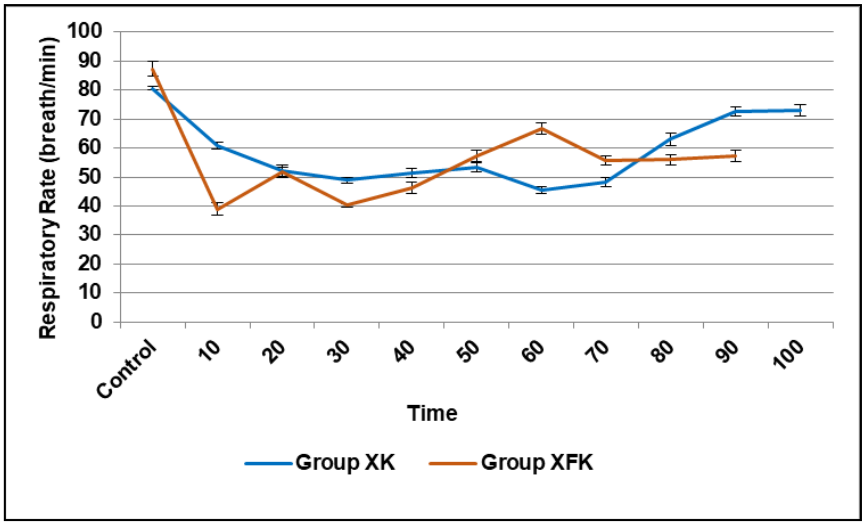

Figure 3. Effects of different anaesthetic combinations on respiratory rate.

Comparison of Different Anaesthetic Regimens on the Reflex Responses in Rabbits

Table 1 shows the effect of various anaesthetic combinations on reflex responses following anaesthesia. Within 1 minute, all of the animals in groups XK and XFK had lost their righting reflex. The animals in group XFK had the quickest loss of righting reflex, and the animals in group XK had the longest loss of palpebral reflex. In the animals of group XK, the pedal reflexes were never fully lost. The animals in group XK had the longest length of righting reflex recovery. The highest withdrawal time of palpebral reflex was found in the animal of group XFK as compared to group XK.

Table 1. Effect of different anaesthetic combinations on the reflex renposes following anaesthesia in rabbits

Group	Loss of Righting Reflex (sec)	Return of Righting Reflex(min)	Loss of Palpebral Reflex (sec)	Return of Palpebral Reflex (min)	Loss of Pedal Reflex(min)	Return of Pedal Reflex (min)
XK	60.5± 0.015	113.5±0.707	60.5±0.015	59± 2.828	-	-
XFK	20.5± 2.121	91.5±3.535	22± 1.414	71± 2.828	12.5± 2.121	37.677±2.081

Comparison of Different Anaesthetic Regimens on the Onset of Induction and Duration of Anaesthesia in Rabbits

The longest induction period as well as the highest duration of anaesthesia was found in the animals of group XK (Table 2).

Table 2. Effect of different anaesthetic combinations in rabbits on the onset of induction and duration of anaesthesia

Anaesthetic Combinations	Onset of Induction Time (sec)	Duration of Anaesthesia (hr)
XK	60.5± 0.015	1.75±0.353
XFK	20.5± 2.121	1.425±0.035

Effect of Different Anaesthetic Combinations on Biochemical Parameters in Rabbit

Effects of anaesthetic combinations on some biochemical parameters (Total protein, albumin, globulin, creatinine, cholesterol, triglyceride, HDL, LDL, sodium, potassium, calcium, phosphorus, chloride) in rabbits are shown in Table 3.

At 30 minutes, we observed no significant change in the total protein value in the animals in group XK. When compared to the preanaesthetic control value, the value of TP in group XFK was considerably (P<0.05) lower at 30 minutes during anaesthesia.

At 30 minutes after induction, the blood albumin level in the animals of group XK was substantially (P<0.05) greater than the preanaesthetic control values. At 30 minutes following induction of anaesthesia, we found no significant changes in serum albumin levels in the animals in group XFK.

When compared to preanaesthetic control values, the value of creatinine in the animals of group XFK was considerably (P<0.05) lower at 30 minutes. At 30 minutes following induction of anaesthesia, we found no significant changes in the levels of creatinine in the animals in group XK.

At 30 minutes, the serum cholesterol level in group XK animals was significantly (P<0.05) higher. Whereas at 30 minutes after induction, the cholesterol level in group XFK animals was considerably (P<0.05) lower than the preanaesthetic control values.

When compared to preanesthetic control values, the value of triglyceride in the animals of groups XK and XFK was considerably (P<0.05) lower at 30 minutes.

When compared to preanaesthetic control values, the HDL and LDL levels in group XK animals were significantly (P<0.05) higher at 30 minutes. At 30 minutes after induction, the value of HDL in the animals of group XFK was considerably (P<0.05) lower.

The value of sodium in the animals of group XK was found to be considerably (P<0.05) lower at 30 minutes after induction in this investigation. At 30 minutes after induction, the sodium and potassium levels in the animals in group XFK were significantly (P<0.05) higher. At 30 minutes after induction, we found no significant changes in potassium in the animals of group XK.

At 30 minutes, the calcium value in the animals of group XK was considerably (P<0.05) decreased, while the calcium value in the animals of group XFK was significantly (P<0.05) increased. At 30 minutes, the calcium and phosphorus values in the animals of group XFK were substantially (P<0.05) greater than the preanaesthetic control value.

When compared to preanaesthetic control values, the value of chloride in the animals of groups XK and XFK was considerably (P<0.05) lower 30 minutes after induction.

Table 3. Effects of different anaesthetic combinations on some serum biochemical parameters in rabbits

Parameter	Group	Preanaesthetic Control	30 min after induction
1. Total protein (gm/dl)	XK	6.357± 0.04[a]	6.287± 0.025 [a]
	XFK	6.492± 0.33 [a]	5.467± 0.028[b]
2. Albumin (gm/dl)	XK	3.324± 0.015 [a]	3.48± 0.01 [b]
	XFK	3.38±0.31[a]	2.87± 0.02 [a]
3. Creatinine (mg/dl)	XK	1.434±0.063 [a]	1.34± 0.037 [a]
	XFK	1.48±0.05 [a]	1.26± 0.037 [b]
4. Cholesterol (mg/dl)	XK	94.443± 0.025 [a]	106.06± 0.142 [b]
	XFK	94.60± 1.0 [a]	80.77 ±0.497 [b]
5. Triglyceride (mg/dl)	XK	83.734 ± 0.352 [a]	82.947± 0.160 [b]
	XFK	82.7± 1.91 [a]	69.64± 0.056 [b]

6. HDL (mg/dl)	XK	44.443± 0.030 [a]	52.034 ± 0.153 [b]
	XFK	44.15±0.26 [a]	28.68± 0.05 [b]
7. LDL (mg/dl)	XK	33.517± 0.256 [a]	37.484± 0.041 [b]
	XFK	33.25±0.52 [a]	35.2± 0.05 [b]
8. Sodium (mmol/l)	XK	155.463± 0.508 [a]	147.8± 0.556 [b]
	XFK	154.28±1.00 [a]	158.967± 0.929 [b]
9. Potassium (mmol/l)	XK	4.72± 0.056 [a]	4.3± 0.2 [a]
	XFK	4.58±0.161 [a]	3.59± 0.04 [b]
10. Calcium (mg/dl)	XK	9.72± 0.135 [a]	8.713± 0.036 [b]
	XFK	9.33± 0.55 [a]	10.75± 0.087 [b]
11. Phosphorus (mg/dl)	XK	2.7967± 0.085 [a]	3.914± 0.045 [b]
	XFK	2.59±0.41 [a]	3.66± 0.053 [b]
12. Chloride (mmol/l)	XK	107.234 ± 0.352 [a]	106.134 ± 0.153 [b]
	XFK	107.18±0.28 [a]	105.467 ± 0.252 [b]

DISCUSSION

Throughout the anaesthetic period, there were no significant changes in rectal temperature in group XK in this investigation. Similar findings have been reported by others (Oguntoye and Oke, 2014). In group XFK, however, the rectal temperature was considerably higher at 20 and 30 minutes compared to preanaesthetic control values. The increase in body temperature could be due to anesthetics (xylazine, fentanyl, ketamine) eliciting the thermoregulatory center and causing animals to become hyperthermic (Afshar et al., 2005).

Heart rate reduced significantly from 10 to 60 minutes (group XK) and 40 to 80 minutes (group XFK) compared to preanaesthetic control values, then increased and returned to baseline values in group XK and group XFK animals at 100 minutes. This conclusion was in line with the findings of (Afshar et al.,2005). When xylazine is given, it causes peripheral vasoconstriction, which causes an increase in arterial blood pressure and a drop-in heart rate (Kaya et al., 2002).

In this investigation, the RR was first reduced from its preanaesthetic control values, then fluctuated up to recovery in all groups of animals. According to (Kamal et al., 2019) and Murrell (2007), xylazine's respiratory effects are normally clinically negligible, but it can cause respiratory depression, with a decrease in tidal volume and respiratory rate, when used in combination with other medicines.

Because no surgery was conducted in this investigation, the surgical anaesthetic duration was measured using the righting reflex, palpebral reflex, and pedal withdrawal reflex, as described in the literature. In adult rabbits, Karasu et al. (2018) and Bienert et al. (2014) found that reflex loss and return periods varied according to the dose of anaesthetic regimens, with stronger doses providing longer sedation durations and longer pedal withdrawal reflex return times.

In this investigation, we found that after 30 minutes, the values of TP and albumin in all groups of animals were lower than their preanaesthetized control values. Gil et al. (2004) found that TP and albumin levels in rabbits

decreased under intramuscular anaesthesia, which is consistent with this finding. The decrease in TP, albumin, and globulin in this study could be related to anaesthetic drug haemodilution and haemodynamic alterations in cell membrane permeability. When compared to preanaesthetic control values, serum creatinine levels in group XFK were lower at 30 minutes. In contrast to our findings, Gil et al. (2004) observed an increase in serum creatinine levels 30 minutes following the treatment of Xylazine-ketamine to rabbits. However, in this investigation, lower creatinine concentrations could be linked to the anesthetics' short-term effects on renal function.

The liver and the stress response have a direct impact on serum cholesterol levels (Akter et al., 2020). At 30 minutes after induction, blood cholesterol levels were considerably lower in group XK and significantly higher in group XFK in this investigation. Similar findings have been reported by others (Gil et al., 2004). Lipolysis caused an increase in serum cholesterol levels. The most frequent kind of lipid storage is triglycerides, which are an important source of energy. The triglyceride value in the animals of groups XK and XFK was considerably lower at 30 minutes. This result is reliable to the findings of (Gil et al., 2004).

In all groups, the HDL value was considerably lower at 30 minutes compared to preanaesthetic control values. In all groups, the LDL value was considerably higher at 30 minutes compared to preanaesthetic control values. Similar findings have been reported by others (Perumal et al., 2007). Because ketamine promotes sympathetic nerve activity, ketamine anesthesia decreased serum HDL levels while increasing serum LDL levels (Akter et al., 2020).

The value of sodium was decreased in group XK and raised in group XFK in this investigation, which corresponded with the findings of the previous study (Gil et al., 2004). As a result, the elevated serum sodium concentrations are probably linked to a decrease in renal blood flow. Potassium levels in all groups of animals were lower than preanaesthetic control levels. Rahman et al. (2021) found a considerable increase in serum potassium levels after ketamine–xylazine injection compared to control levels; this increase was likely due to the impact of xylazine, an alpha 2-adrenoceptor agonist, which contradicted this conclusion.

The calcium value in the animal group XK declined at 30 minutes from the pre-anaesthetized control value, which is similar to the findings of another study (Khalaf et al., 2014). However, when compared to preanaesthetic control values, the calcium level in group XFK animals was higher at 30 minutes. Similar findings have been reported by others (Kamal et al., 2019). Rapid mobilization of calcium following the xylazine-ketamine-related influence on renal function could explain the significant increase in serum calcium levels. All groups' serum phosphorus concentrations were higher at 30 minutes than preanaesthetic control values, which is consistent to the findings of (Karasu et al., 2018). In comparison to preanaesthetic control values, serum chloride concentrations in groups XK and XFK dropped.

CONCLUSION

Our findings suggest that xylazine-ketamine induced sufficient depth and duration of anaesthesia compared to xylazine-fentanyl-ketamine. For surgical treatments, the longer anaesthetic duration may be advantageous. When planning an invasive rabbit study, researchers should take into account the alterations in serum biochemical parameters caused by this combination.

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Ethical approval:

This animal work was carried out in accordance with the guidelines and approval of the Animal Welfare, Experimentation and Ethics Committee (AWEEC) of the Faculty of Veterinary Science, Bangladesh Agricultural University, Mymensingh [Permission Number: AWEEC/BAU/2021 (45)].

Conflict of interest:

No conflict of interest.

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